



When bad gets worse: Pleural effusion after liver transplantation

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Abstract: Liver transplantation became the standard therapy for acute and chronic liver failures of any etiology to date, with a history of over 80,000 procedures performed. The main challenge remains the limited number of donors. Standardization of waiting lists, efficient prioritization of recipients, strict adherence to ethical rules, and appropriate pre- and postoperative management are essential criteria for the development of liver harvesting and transplantation centers. Our study focuses on postoperative pulmonary complications, with pleural effusions being common and impacting the patient's outcome.

Keywords: transplant liver; pulmonary; pleural effusion

1. Introduction

The first liver transplant was performed in 1967 in the United States by Thomas Starzl. A year later, the first liver transplant in Europe took place, performed by Roy Calne in Cambridge. Since then, liver transplantation has become a standard therapy for acute and chronic liver failures of any etiology, with over 80,000 procedures performed to date. Survival rates have gradually improved over the past 25 years, reaching 96% in the first-year post-transplant and 71% at 10 years after transplantation. [1,2,3]

The present study aims to evaluate post-surgical respiratory complications, particularly pleural effusions. Various markers are being

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assessed to determine their impact on the subsequent progression of patients. The importance of pleural fluid type, biochemical and cytological analysis, the necessity, and timing of drain tube implantation are being investigated.

2. Materials and Methods

This review was conducted through a detailed evaluation of existing articles debating the liver transplantation. A systematic search of literature was performed using database (PubMed).3.

3. Liver Transplantation

3.1 Generalities

A procedure considered heroic in its early - days, liver transplantation (LT) has made significant progress in the last 30 years. The credit goes to the teams that have been operating since the beginning. Skepticism from potential donors' families, lack of trust from potential recipients, the novelty factor, lack of standardization in case selection, technique, and post-operative management could have led to abandonment. Perseverance, on the other hand, has led to the refinement of the procedure, a significant and consistent increase in the number of interventions, reduction in complications and graft rejection rates, and increased one-year survival rates. Selection criteria have seen significant improvements, focusing on maximizing benefits for the recipient.[4] It remains a procedure of major complexity, involving both medical and psychological impact. Each patient represents a distinct entity with different emotional characteristics, requiring constant and effective collaboration between the medical team and a dedicated psychologist. The medical risks involved, as well as the emotional changes the patient will go through, are equally important. Challenges arise prior to liver transplantation surgery. Donor and recipient variables require careful investigation to achieve optimal outcomes. Transplant indications and symptoms of liver failure must be thoroughly assessed, including ascites, gastrointestinal variceal bleeding, hepatic encephalopathy, and the consequences of malnutrition.

3.2. Orthotopic Liver Transplantation

Orthotopic liver transplantation (OLT) is the standard procedure for liver transplantation. It

involves the complete removal of the recipient's diseased liver and the implantation of a healthy liver from a deceased or living donor in its anatomically correct position. The surgical technique includes careful dissection of blood vessels, bile ducts, and hepatic structures to ensure proper vascular and biliary anastomoses. The success of orthotopic liver transplantation depends on meticulous surgical planning, coordination of the transplant team, and postoperative care to prevent complications and ensure graft viability. A major challenge in liver transplantation field is the insufficient number of donors compared with the growing demand of transplant candidates. Thus, we emphasize that appropriated donor/receptor selection, allocation and organ preservation topics should contribute to improve the number and outcomes in liver transplantation. [5]

Successful transplant outcomes require optimal patient selection and timing. The limited availability of organs has led to long waiting periods for liver transplantation and consequently many patients become seriously ill or die while on the waiting list. This has major implications in the selection of patients, as well as the timing of transplant, for optimal use of these scarce organs. Indications and contraindications have changed slightly over the years. [6]

Nowadays, the intervention has excellent results. The survival rate is 90% at 1 year and 80% at 5 years. The improvement in the composition of the recipient list, accurate selection of candidates, advancements in technique, and management of complications have made this outcome possible. The indications for liver transplantation have now been expanded. Generally, priority is given to patients with liver cirrhosis and a high MELD score.

The management of patients on the waiting list is of prime importance to avoid death and drop out from the waiting list as well as to improve post-transplant survival rates. There is a diversity of patients on the waiting list for transplantation and equity should be preserved between those with cirrhosis of high and intermediate severity and those with HCC. For the more severe cases who may swiftly access liver transplantation, it is essential to rapidly

determine whether liver transplantation is indeed indicated, and to organize a fast workup ahead of this. For patients with HCC, a bridge therapy is frequently required to avoid progression of HCC and to maintain patients within the criteria of liver transplantation as well as to reduce the risk of post-transplant recurrence of HCC. For patients with cirrhosis and intermediate MELD score, waiting time can exceed 1 year; therefore, regular follow-up and management are essential to maintain the patient alive on the waiting list and to achieve a good survival after liver transplantation.[7]

3.3. Liver transplantation and the pandemic

The issue of COVID-19 occupied the agenda of the whole world, from 2020 till present. The pivot of this pandemic was a crucial element, that became almost as important as the virus itself, namely the lockdown. In an article about the pandemic lockdown, healthcare policies and human rights, it is mentioned “the greater good”. Of course, the major objective of quarantine was to reduce contagion or spread the disease. Reliable studies have demonstrated the significant impact on the spread of SARS COV-2. [8] But also, we should consider the other face of the situation. While the whole world was focused on identifying optimal preventive measures and promoting telemedicine or at least outpatient care, patient accessibility and availability dramatically decreased. Elective surgeries suffered greatly. The approach and completion of liver transplant lists, patient evaluations to establish inclusion criteria, and the transplant procedures themselves were minimized. Precious time was lost, and some patients who could have benefited unfortunately passed away. So, it was a total eclipse of all other diseases, under the influence of COVID-19 pandemic.[8] The effect of coronavirus disease 2019 (COVID-19) on liver transplantation procedures and recipients is still not completely understood but overall involves the risk of donor-derived transmission, the reliability of diagnostic tests, health-care resource utilization and the effect of immunosuppression.[9] Cases of liver damage or dysfunction (mainly characterized by moderately elevated serum aspartate

aminotransferase levels) have been reported among patients with COVID-19. However, it is currently uncertain whether the COVID-19 related liver damage/dysfunction is due mainly to the viral infection by itself or other coexisting conditions, such as the use of potentially hepatotoxic medications and the coexistence of systemic inflammatory response, respiratory distress syndrome-induced hypoxia, and multiple organ dysfunction.

Individuals at high risk for severe COVID-19 are typical of older age and/or present with comorbid conditions such as diabetes, cardiovascular disease, and hypertension. This is also the same profile for those at increased risk for unrecognized underlying liver disease, especially nonalcoholic fatty liver disease. This could make them more susceptible to liver injury from the virus, medications used in supportive management, or hypoxia. [10]

3.4. Liver-lung relationship

What about the smoking and the liver?

The detrimental effects of smoking on the liver are not sufficiently debated till present. Smoking affects liver on 3 separate mechanisms: toxic (direct and indirect), immunologic and oncogenic. There is an emerging body of evidence of an association between cigarette smoking and progression of fibrosis in chronic liver diseases such as nonalcoholic fatty liver disease and primary biliary cholangitis. Smoking is associated with accelerated development of hepatocellular carcinoma in patients with chronic hepatitis B or C virus infection. Tobacco smoking adversely affects lung function, which increases physical limitations and may preclude liver transplantation. Following liver transplantation, smoking is associated with several adverse outcomes, including increased risk of de novo malignancy, vascular complications, and nongraft-associated mortality.[11] Smoking cessation is the only intervention proved to reduce the lung function decline. [12] So, it will no longer be a risk factor for liver damage.

Hospitalizations, chronic respiratory disease exacerbations, and regular checkups constitute ideal moments to arrange smoking cessation interventions. When nicotine dependence is severe, specialized smoking

cessation interventions using various types of therapies should be used. [12] The respiratory illness caused by the novel coronavirus disease serves as a good example of the complex interplay between the lungs and the liver. It is evident that cigarette smoking has important negative effects on a multitude of liver diseases and that patients' smoking cessation must be prioritized. The data are limited, and more research is needed to better understand how smoking affects the liver. Smoking cessation is essential, even in patients with liver disease, considering the risks mentioned above. Even if industry marketing claims the potential of e-cigarettes as an approach for smoking cessation, there is no definitive evidence supporting this claim. They may be useful in suspending conventional smoking. Still, 80% of former smokers continued using e-cigarettes after quitting traditional smoking, thus remaining nicotine addicted. [12]

4. Pulmonary complications: a major challenge

Medicine has made significant progress in the field of liver transplantation. Currently, there is increased enthusiasm for the training and development of organ procurement and transplant teams. The statistical data regarding the growing number of procedures and their success rates are encouraging. Liver transplantation became a routine procedure in some countries and is continuously evolving in others. Patient selection criteria, appropriate case prioritization, technique refinement, and improved postoperative evaluation measures are all showing positive dynamics. As a result, dedicated teams are inclined to choose this intervention as a potentially life-saving option. The surgery is successful in numerous cases. However, the complications that arise during the early or late preoperative period can be less predictable and more challenging to manage. Host-related factors contribute significantly to this disadvantage. Furthermore, the frequent occurrence of pulmonary complications and their impact on the patient's recovery must be taken into account. The risk factors that predispose to their occurrence need to be investigated, and measures to eliminate them need to be found.

Despite knowing the severity of the case, even though it is usually a terminally ill patient, the intervention is elective. The patient is informed about the risks and benefits. The transplant team decides on the optimal timing. A question arises: does the transplant do more harm than good? There are still unknowns. What is the patient's life expectancy without intervention? What is the life expectancy after transplant? Taking into account the possibility of pulmonary complications, which are frequent and have an impact on the outcome, another question arises: would the patient have lived longer if they had not undergone surgery and allowed the underlying disease to run its course?

The rejection of the organs, acute or chronic, secondary infections due to immunosuppression are the most frequent complications. Secondary complications or non-infectious complications arise following the surgical intervention. Pulmonary complications are particularly relevant to morbidity and mortality. They most commonly occur within the first 6 months after graft implantation. Despite significant improvements in surgical techniques, immunosuppression, and intensive care management in recent years, and despite the use of prophylactic antibiotics, there is still a significant rate of pulmonary complications. [13] Considering the high rate of pulmonary complications, the preoperative evaluation of a transplant candidate routinely includes a pulmonary assessment with a standardized battery of investigations. This involves a clinical evaluation of the patient, with a focus on respiratory symptoms, as well as chest radiography (X-ray) and respiratory function tests. This evaluation helps assess the surgical risk. Pre-transplant pulmonary considerations in patients with end-stage hepatic diseases relate primarily to hypoxemia from poorly understood intrapulmonary vascular dilatations, mechanical dysfunction, and states of increased extravascular lung water. Except in severe cases, however, these generally do not prohibit liver transplantation, and even are likely to improve after transplant surgery. Early postoperative complications may be categorized as those expected from extensive intra-abdominal surgery

that requires significant volume resuscitation, which typically are managed in the usual manner for those clinical situations. As immunosuppression begins to have an effect, the LT recipient becomes susceptible to the same opportunistic infectious organisms (with their frequent pulmonary involvement) that cause significant morbidity and mortality in recipients of other solid organ transplants. Because many of the immunosuppressive agents also are the same, noninfectious side effects such as pulmonary edema and malignancy also are similar. As with all immune-compromised patients, prophylaxis, when possible, persistent infection surveillance, and an aggressive diagnostic and therapeutic approach help decrease the impact of pulmonary dysfunction in LT recipients. [14]

Pulmonary complications following orthotopic transplantation are common and, according to existing data up to the present moment, are associated with a negative impact on morbidity and mortality. Post-liver transplantation pulmonary complications can affect both morbidity and mortality often necessitating intensive care during the immediate postoperative period. Poor clinical outcomes have been known to be associated with age, severity of liver dysfunction, and preexisting lung disease as well as perioperative events related to fluid balance, particularly transfusion and fluid volumes. Delineating each and every one of these pulmonary complications and their associated risk factors becomes paramount in guiding specific therapeutic strategies. [15] An early diagnosis of the type of complication constitutes a major prognostic factor in immune-depressed patients. Thus, the practicing pneumologist must thoroughly know the principal respiratory complications of solid organ transplant. Atelectasis, pleural effusion, and pulmonary edema are among the most common complications. On the other hand, the development of a post-transplant infection is more severe and significantly increases the mortality rate. [17] Pleural effusion (PE) is a common complication of orthotopic liver - transplant, reported to occur in 32% to 95% of cases within the first week after transplant. [18] All these respiratory disorders can affect lung

compliance, alveolar gas exchange. In severe cases, tracheal intubation and mechanical ventilation is required. In the early postoperative period, the occurrence of pulmonary complications is associated with a longer duration of intubation, which increases the risk of infection. Prolonged ventilator dependence is associated with increased morbidity, slower recovery, subsequent complications, and may lead to the need for prolonged home ventilation. There are significant preoperative risk factors that can contribute to the occurrence of these events. A pre-existing restrictive syndrome is a significant risk factor. A high MELD score is often associated with the development of pleural effusion, increased transfusion requirements, and a high risk of fluid accumulation. Additionally, restrictive syndromes, muscle atrophy, and severe nutritional deficits often occur. Preoperative ventilator dependence, comorbidities such as diabetes or renal insufficiency, frequently lead to respiratory failure. Numerous intraoperative risk factors are responsible for the development of post-transplant pulmonary complications. These include intraoperative fluid and blood transfusion volume, perioperative fluid balance, common postoperative factors, acute rejection during the hospital stay, and the onset of renal insufficiency. Other factors that should not be overlooked include greater exposure to nosocomial agents, surgical complications, re-intervention, or the need for re-transplantation.

Studies showed that a MELD score higher than 25, an intraoperative fluid transfusion volume more than 10 L, and intraoperative blood transfusion >4 L, were all independent predictors of a pulmonary complication. A fluid balance <300ml on the first two postoperative days appeared to be a protective factor. A greater susceptibility to interstitial lung edema can impair the postoperative oxygenation. The need for ventilation increase.

During the early postoperative period, achieving rapid ventilator weaning is a positive predictive factor. Delayed extubation increases the risk of infection. The presence of hypoalbuminemia, the development of renal failure, and cardiac dysfunction are other reasons

for the occurrence of interstitial edema, reduced pulmonary compliance, increased respiratory effort, and prolonged ventilator dependence. [13]

However, the identification of risk factors is carried out more efficiently, post-transplant monitoring is done at a standardized level, resulting in a consistently increasing one-year survival rate over the past three decades.

Various pulmonary disorders affecting the pleura, lung parenchyma and pulmonary vasculature can occur in the end stage liver disease. They will complicate LT. Recent studies shows that 8% of cirrhotic patients in an intensive care develop at least one pulmonary complication. Hepatopulmonary syndrome (HPS), portopulmonary hypertension (POPH) and hepatic hydrothorax (HH) are the most frequent complications, specific to cirrhosis and portal hypertension. Severe HPS is an indication of LT. The hypoxemia is usually solved after surgery. Severe POPH is a relative contraindication for LT. Moderate one, who improve with therapy, can benefit. Refractory cases of hepatic hydrothorax can also benefit from LT. [19]

4.1. Pleural effusion- when good turns bad?

In order to establish the degree of negative predictive value of post-transplant pleural effusion, this study compares the outcomes of patients who had pleural effusions due to cirrhosis with those who develop it as a postoperative complication. Certain characteristics of pleural effusion are evaluated to determine their influence on the case's progression. Regarding pleural effusion, the goal is to assess predisposing factors, the possibility of elimination them, the patient's progress, and the impact on mortality.

The majority of these effusions are thought to be caused by lymphatic disruption and diaphragmatic defects occurring during hepatectomy, leading to the transfer of fluid from ascites into the pleural space. Exudative effusions can occur with some regularity and up to one-fifth have microorganism identified on culture. Persistent effusions have been associated to worse outcomes. Recurrent effusions have been associated with allograft rejection. The

composition of persistent effusion requiring pleural intervention is more diverse. [18]

Typically, pleural effusion occurring after liver transplantation develops on the right side, and the amount of fluid varies. Usually, the fluid is a transudate and does not develop as a consequence of cardiac dysfunction. In the first week after surgery, the pleural effusion increases in quantity, and then it resolves in the following weeks. It is self-limiting and asymptomatic, and rarely requires thoracentesis or drainage tube placement. However, if it persists, it can cause respiratory failure. Other possible unfavorable outcomes include atelectasis, pneumonia, or more challenging recovery. [13] Both before and after liver transplantation, pleural conditions are of particular importance.

Post-transplant pleural effusion is related to the duration and type of immunosuppression, and most studies show that it is not a sign of hepatic dysfunction. Organ-specific pleural complications include pleural effusion from hepatic veno-occlusive disease. [20] Most commonly, pleural effusion occurs on the right side. In a study conducted on 11 patients, all of them developed right-sided pleural effusion post-transplant, and 4 of them also had associated left-sided pleural effusion. [21] Another research study, involving 135 patients, evaluates the radiological findings in each subject. Personal respiratory history and specific respiratory symptoms are taken into account. The most common radiographic abnormality was elevated right hemidiaphragm in 32 patients (23.7%), followed by pleural effusion in 22 (16.2%), atelectasis in 21 (15.5%), hilar enlargement in 18 (13.3%), and elevated left hemidiaphragm in 9 (6.6%). Seventeen of 22 patients (77.3%) had right pleural effusion, 4 (18.2%) had bilateral, and 1 (4.5%) had left pleural effusion. Of the 10 patients undergoing thoracentesis, 9 had transudates and 1 had an exudate. [22]

The results of a prospective study published in 2014 show that a significant number of patients on transplant waiting lists develop pleural effusions. The majority of these effusions are transudative in nature and predominantly localized on the right side. A total of 135 individuals were evaluated, all of whom

underwent chest radiography. Among them, 16 presented with respiratory symptoms prior to the intervention, and 49 of the chest radiographs showed abnormalities. Of the pleural effusions observed, 77.3% were on the right side, 18.2% were bilateral, and 4.5% were on the left side. Thoracentesis was performed in 10 cases, with 9 of the patients having a transudative pleural fluid.[23]

A recent study conducted on 1602 liver transplant patients identified 124 cases of persistent pleural effusion occurring more than 30 days after the surgical intervention. Correlations were made based on the type of fluid (exudate or transudate), biochemical or cytological examination. 90.2% of patients developed exudative pleural effusion, subcategorized based on the level of LDH or proteins. Overall, the two-year survival rate was lower compared to patients who did not have a pleural reaction. Cytological examination correlated with subsequent progression. One-year mortality was associated with the presence of erythrocytes in the pleural fluid. The predominance of neutrophils was associated with a slower progressive course: slower weaning from the ventilator, the need for vasopressor support, and surgical debridement intervention. Thus, in the cited study, pleural effusion complicating liver transplantation has a negative impact on mortality, and certain markers serve as predictors of a favorable slow progression. [24]

The postoperative respiratory conditions of the recipients are analyzed. They will be associated with the clinical outcomes, including length of stay. Referring to this pulmonary complication, in association to the liver transplantation, it is mandatory to exam: time to extubation, significant pleural effusion, and initial postoperative PaO₂/FiO₂ ratio. Recent studies have shown that the duration of intensive care unit (ICU) hospitalization is longer in patients who present with massive intraoperative transfusion, extubation beyond 24 hours, and low initial PaO₂/FiO₂ ratio. A research study conducted on 22 pediatric patients analyzed various aspects related to the outcomes of transplant recipients. Half of the subjects were extubated more than 24 hours after the surgery.

Eight patients developed pleural effusions that required drainage. Massive blood transfusion was associated with the development of pleural effusion. This aspect also appeared to influence the duration of intubation and prolonged stay in the ICU. Certain correlations can be made between the postoperative PaO₂/FiO₂ ratio, which depends on age, severity of liver impairment, and the need for intraoperative blood transfusion. [25]

A retrospective study conducted between 2001 and 2014 confirms that the occurrence of pulmonary complications within the first 30 days after liver transplantation increases the rate of failure. It also certifies that early detection and treatment can improve survival chances. Out of the 204 included patients, 46 received grafts from brain-dead donors, while the rest received grafts from living donors. Among the subjects, 161 manifested pulmonary complications from the initial postoperative evaluation. [26]

Recent literature shows that the presence of pleural effusion in transplant recipients is a negative predictive factor for the occurrence of pulmonary infections. Changes in the laboratory parameters (inflammatory syndrome, increased levels of Interleukine6 (IL-6), IL-8, Tumor necrotic factor (TNF)-alpha occur in patients with pleural effusion. Given these aspects, a rigorous approach to the prevention of pulmonary infections is recommended for these subjects. [27]

Posttransplant pleural effusion is related to the duration and type of immunosuppression, and most studies show that it is not a sign of hepatic dysfunction. Organ-specific pleural complications include pleural effusion from hepatic veno-occlusive disease. [20] Most commonly, pleural effusion occurs on the right side. In a study conducted on 11 patients, all of them developed right-sided pleural effusion post-transplant, and 4 of them also had associated left-sided pleural effusion. [21]

TL (trapped lung) is a complication of persistent pleural effusion, defined by chronic lung atelectasis. Trapped lung is less associated with end-stage liver disease, although a few studies have shown it to be a complication of hepatic hydrothorax. Trapped lung and pleural

involvement are negative predictive factors for the patient's transplant outcome.

In a study conducted from 2006 to 2015 at the Ronald Reagan UCLA Medical Center, a renowned transplant center, patients who developed pleural effusion between 1- and 18-months post-operation, requiring thoracentesis or surgical intervention, were included. The cases were divided into two subgroups: those with trapped lung and those with persistent pleural effusion in the first-year post-operation. Trapped lung was defined as the permanent impairment of the pleura resulting in lung non-expansion (leading to ex-vacuo pneumothorax or hydropneumothorax).

The incidence of trapped lung among patients with persistent pleural effusion after transplantation was 21.4%. 4% of patients had evidence of trapped lung prior to transplantation. The one-year survival rate was 78% for patients with persistent pleural effusion. The study showed that those with trapped lung had a higher risk of mortality (HR 2.47, 95% CI 1.59-3.82, $p < 0.001$). The duration of hospitalization was longer for those with trapped lung. This group required more surgical interventions and had a higher rate of overall pleural procedures. Ventilator dependency was similar between the two groups. [28]

In a retrospective study conducted on 374 liver transplant recipients, 189 developed pleural effusion in the early postoperative period. Those with pleural effusion had low levels of fibrinogen, total proteins, and hemoglobin. No notable differences were observed in one-year mortality among patients with pleural effusion. [29] On the other hand, a study has emerged indicating a higher mortality rate among patients who develop pleural effusions. It was conducted on 1602 liver transplant patients, and there was identified 124 cases of persistent pleural effusion occurring more than 30 days after the surgical intervention. Correlations were made based on the type of fluid (exudate or transudate), biochemical or cytological examination. 90.2% of patients developed exudative pleural effusion, subcategorized based on the level of LDH or proteins. Overall, the two-year survival rate was lower compared to patients who did not have a

pleural reaction. Cytological examination correlated with subsequent progression. One-year mortality was associated with the presence of erythrocytes in the pleural fluid. The predominance of neutrophils was associated with a slower progressive course: slower weaning from the ventilator, the need for vasopressor support, and surgical debridement intervention. Thus, in the cited study, pleural effusion complicating liver transplantation has a negative impact on mortality, and certain markers serve as predictors of a favorable slow progression. [24]

Not always, but the placement of a drainage tube is sometimes necessary. There are studies investigating whether this aspect plays a determining role in the prognosis of transplant patients. In research conducted between 2009 and 2016, 597 patients who developed pleural effusions within the first 10 days of surgery were evaluated. Among them, 361 required the placement of at least one drainage tube. Those with a MELD score above 25 were more frequently affected (75.7% vs. 56%). The aim of the study is to differentiate between early tube implantation at the time of surgery or delayed placement at the onset of pleural effusion. 97% of patients underwent right-sided drainage tube implantation.

A significant number of patients who were drained in the intensive care unit required optimization of coagulation before the procedure. Out of the cases, 15 experienced hemorrhages and 6 had pneumothorax that required drainage. Significantly fewer complications were observed in cases where the drainage tube was placed in the operating room. Therefore, we conclude that for patients with risk factors, the placement of the drainage tube should be performed in the operating room. [30]

In a 4-year retrospective study conducted on 512 patients who underwent liver transplantation, cases of radiologically evident pleural effusion within 30 days before or after the procedure were evaluated. The study aimed to assess hospitalization duration, rehospitalization rates, need for home oxygen, and 1-year survival. 21% of patients developed pleural effusion, with 10% occurring pre-transplant, 18% post-transplant, and 36% in both situations.

Characteristics associated with the presence of any pleural effusion included an increasing model for end-stage liver disease score, re-transplantation, diagnosis of alcoholic liver disease, low protein levels, and sarcopenia. Effusion patients had longer hospital stays (17 vs 9 days) and higher likelihood of discharge to a care facility (48% vs 21%). Ninety-day readmission occurred in 69% of effusion patients (vs 44%). One-year patient survival with any effusion was 86% (vs 94%). [31] With a similar purpose, a study conducted on a group of 114 recipients of orthotopic transplantation evaluates certain parameters such as the cause of hepatic impairment, respiratory function tests, arterial blood gas analyses, duration of the surgical procedure, length of stay in the intensive care unit, total hospitalization duration, pulmonary complications, and causes of mortality. 48 patients developed pulmonary complications, directly impacting survival. 45.6% of patients were smokers, a significant predictor of respiratory impairment. There was no relation between pulmonary function test results and orthodeoxia and pulmonary complications and mortality. Early and late survival rates were significantly lower in patients in whom a microorganism was isolated on deep tracheal aspirate culture, while early survival was significantly reduced in the presence of a pleural effusion. [32]

A particularity is represented by pediatric liver transplantation. Small amounts of fluid accumulate both in the peritoneal and pleural spaces. Occasionally, when large quantities of fluid are present, pleural drainage is necessary. We are discussing a study conducted on 164 children (184 liver grafts). Out of these, 31 cases developed excessive fluid collections. There were 19 cases of pleural effusion, 8 cases of ascites, and 4 cases of both pleural effusion and ascites. Pleural effusions occurred between days 1-44 after transplantation, while ascites occurred between days 1-14. Radiological diagnosis was established in 91% of pleural effusion cases and in 10% of ascites cases. When comparing interventional treatment methods (guided or unguided radiological drainage, surgical

intervention), no significant differences were established regarding the outcome.

Different markers have been investigated in relation to pleural effusion in transplant patients, aiming to establish their role as predictive factors. Thus, the nutritional status of the subjects included in a retrospective study conducted over a 4-year period is analyzed. The duration of hospitalization, the need for rehospitalization, the requirement for home oxygen therapy, and the one-year survival rate are being monitored. Out of the 512 included patients, 107 developed pleural effusion (49 before the intervention, 91 after transplantation, and 32 both before and after the intervention). The duration of hospitalization, the need for readmission, and one-year survival were negatively influenced by the presence of pleural effusion. The study demonstrates that a higher MELD score, chronic ethanol consumption, malnutrition, and sarcopenia are risk factors for the development of pleural effusion in transplant patients. [33]

In a patient with no cardiopulmonary disease and portal hypertension, pleural effusion occurs as hepatic hydrothorax (HH). The estimated prevalence is 5-6%, if we are talking about patients with liver cirrhosis. The ascitic fluid moves from the intraperitoneal space into the pleural space. Thoracentesis and pleural fluid analysis are mandatory. If the liquid gets infected, we are talking about a spontaneous bacterial empyema. [34] Patients with HH can be asymptomatic or present with pulmonary symptoms such as: cough, hypoxemia, respiratory failure. Empyema manifests with increased pleural fluid neutrophils or a positive bacterial culture. [35]

Hemothorax is a particular condition. Despite rare, hemothorax is a severe, mainly iatrogenic and life-threatening complication. Even is not enough studied in LT, it's good to know that it's appearance could and should be prevented. Thoracentesis is the main cause, usually. Studies shows that many patients develop thoracic complications after HT treatment. The mortality rate increase. Also, the median stay in Intensive Care Unit increase. [36]

4.2. Early detection of pulmonary complications – an advantage?

The onset of respiratory symptoms in a patient proposed for transplantation, especially after the intervention, justifies the performance of diagnostic steps. Chest radiography is the first-line approach. A study conducted over an 11-year period evaluates radiologically 300 patients out of the 333 transplanted. Atelectasis and pleural effusion are detected in 86.7% of cases, and pulmonary edema in 44.7%, all developed within the first week after the intervention. Although less common, pneumonia is accompanied by a mortality rate of 36.6%. Furthermore, the study shows that non-infectious complications represent a risk factor for the development of infectious complications. Secondly, a longer dependence on a ventilator is another risk factor. [14] Chest radiography is recommended immediately after anesthesia induction and prior to the intervention. It plays a role in determining the positions of central venous catheters and the endotracheal tube. Early detection of pleural fluid accumulation is possible. We refer to the case of two patients who developed right-sided pleural effusion post-transplantation. Three days before the surgery, chest radiography was performed on the first patient and showed no changes. On the other hand, the second patient had pleural effusion. Pleural drainage was performed prior to transplantation. After anesthesia induction, chest radiography is performed to assess the position of central venous catheters and the endotracheal tube. In both cases, massive pleural effusion is observed in the right lung. Following laparotomy, 2000 ml of transudative fluid is drained through the right diaphragm. In the second patient, fluid accumulation occurred due to the strangulation of the pigtail drainage tube during the transfer of the patient to the operating room. Upon opening the tube, 2000 ml of fluid were drained. Both patients had a favorable outcome (two cases of massive). In cases where pleural effusion is visualized on radiography, thoracic ultrasound is performed.

Ultrasound (US) guidance is currently used for placement of wire-guided thoracic drains, and its use is associated with a decreased risk of complications. Real-time US-guided pleural-space puncture, followed by placement of a pigtail catheter for drainage of effusion, is safe to use and has a high rate of technical success. The

aim of a retrospective study was to report the technical success and complication rates observed during real-time US-guided placement of a thoracic pigtail catheter in pediatric liver-transplant recipients with symptomatic pleural effusion. The study included 25 patients. Seventeen procedures had been performed in the intensive care unit, and 8, in patients undergoing mechanical ventilation. There were 41 pigtail catheter-placement procedures during the study period. 12 patients had altered hemostasis. The technical success rate was 100%, with no major complications such as pneumothorax or hemothorax. Accidental dislocation of the catheter occurred in four patients (9%) over 3-10 days after the first procedure. [37]

The utility of ultrasound-guided diaphragmatic thickness in the preoperative period in healthy controls scheduled for live-related donor hepatectomy and patients suffering from chronic liver disease scheduled for liver transplantation is often evaluated lately. Studies want to highlight its use as a predictor of postoperative weaning failure. In this regard, we present the results of a prospective observational study conducted on 65 patients (30 healthy donors and 35 liver transplant recipients). Right diaphragmatic thickness of both donors and recipients was measured by B-mode ultrasound using a 10 MHz linear array transducer in the supine position in the operation theater just before induction of anesthesia. The duration of ventilator is measured. Recipient patients are divided into two groups: diaphragmatic thickness < 2 mm, and >2mm. Thickness is decreased in patients with chronic liver disease patients as compared to healthy donors. Higher duration of mechanical ventilation was associated with diaphragmatic thickness < 2 mm. [38]

Chest Computer tomography (CT) examination is not routinely used in cases of post-transplant pulmonary complications. Despite its high specificity and sensitivity, it lacks accuracy in determining the type of pneumonia, the nature of pleural effusion, or differentiating atelectasis from inflammatory parenchymal consolidation. However, when correlated with clinical data, it plays a role in further detailing the radiologically

visualized lesions. These aspects are demonstrated by a study conducted on 152 patients examined through chest CT. 29% of the examinations were performed due to clinical symptoms, 20.4% following abnormal radiographs, 42.1% for both reasons, and 7.9% of CT scans were performed without knowing the motivation. [39] Differential diagnosis between subdiaphragmatic fluid accumulation (ascites) and supradiaphragmatic fluid accumulation (pleural effusion) can be challenging. When the fluid is present in both locations, it is difficult to differentiate based on a chest radiograph alone. Basal trapped pleural effusion can lead to confusion. Chest CT examination and thoracic ultrasound are essential in such cases. There are four specific signs indicating pleural fluid accumulation: the diaphragm sign, the displaced crus sign, the interface sign, and the bare area sign. The ultrasound examination identifies pleural fluid accumulation through three of the four signs: the diaphragm sign, the displaced crus sign, and the bare area sign. [40] On CT, the presence of fluid anterior to the crus indicates an intraperitoneal component. The medial location of the posterior recess of the fluid collection and intercostal bulging along its lateral margin suggest a pleural effusion. [41] Accurate localization of peri-diaphragmatic fluid relies on identifying the hemidiaphragms. Pulmonary consolidation and pleural fluid collections are found adjacent and peripheral to the convexity of the hemidiaphragms. On the right side, intraperitoneal fluid is prevented from contacting the bare area of the liver by the coronary ligaments. [39]

5. Liver transplantation – controversial, in the end?

It begs the question of to what extent liver transplantation is ultimately controversial. Beyond the "scientific" aspect of this work, we open an invitation for debate. The psychological component is involved in two directions. Firstly, the patient must receive counseling. They benefit from comprehensive medical explanations provided by doctors, backed by scientific arguments. They are informed about the associated risks and learn about the steps of the intervention and postoperative recovery. They

make an informed decision and sign an informed consent form. However, fears and the fear of the unknown still linger. Here comes the team of psychologists, meant to guide him. But the fears of the medical team are numerous as well. This is where the debate arises. Considering the risks of developing pulmonary complications and the patient's subsequent progression, does the intervention make sense? Does it lose value, given these elements of negative predictability? Does it decrease the interest of the retrieval and transplant teams? Do we still want to carry out such a large-scale intervention burdened by the possibility of doing more harm than good? Ultimately, the guideline is to opt for the therapeutic option with the lowest risks and the highest benefits. The present research aims to provide a systematic, comprehensive, and detailed evaluation of possible pulmonary complications, with a focus on pleural effusion. The ultimate goal is to determine their impact on the transplant recipient's outcome. Essentially, prevention and risk minimization are attempted. We are discussing the patient with end-stage liver disease, whose only curative therapeutic method is the liver transplantation.

6. Discussion:

The present paper addresses a novel, controversial element that has not been sufficiently addressed thus far in relation to the necessity of liver transplantation development. Due to management errors, ranging from the compilation of recipient lists, prioritization, and selection methods, to inadequate pre- and post-intervention evaluations, liver procurement and transplantation still face numerous difficulties worldwide. This paper focuses on pulmonary complications, particularly pleural effusions developed in liver transplant recipients. Certain correlations are established between various clinical and paraclinical parameters, which become markers of the patient's progress post-transplantation.

We believe that the observed aspects will provide fundamental information regarding the progression of the transplant recipient and serve as the basis for further research in this innovative field.

7. Conclusions:

Although the greatest challenge in organ procurement and transplantation, in general, remains the shortage of donors, progress can be made through improved management. Effective prioritization, standardization of pre- and post-operative evaluations, and detailed research on potential post-intervention complications are the foundation for therapeutic success. This research aims to highlight some predictive elements of the progression of liver transplant patients, with a focus on postoperative pleural effusion characteristics. By having a detailed understanding of the risk and addressing them through the evaluation of all negative predictive factors, the study aims to achieve several objectives. It seeks to assess to what extent the benefits of the method are nullified by the intervention-related complications. It aims to estimate when and if the curative potential of the method is lost. It also intends to investigate whether this aspect can be avoided.

Conflicts of Interest: The authors declare no conflict of interest.

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